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METHODS FOR TREATING CARDIOVASULAR DISEASES WITH BOTULINUM TOXIN

by

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BACKGROUND

The present invention relates to methods of preventing or reducing restenosis that may occur in blood vessels after mechanically expanding the diameter of an occluded blood vessel.

Atherosclerosis is a progressive disease wherein fatty, fibrous, calcific, or thrombotic deposits produce atheromatous plaques, within and beneath the intima which is the innermost layer of arteries. Atherosclerosis tends to involve large and medium sized arteries. The most commonly affected are the aorta, iliac, femoral, coronary, and cerebral arteries. Clinical symptoms occur because the mass of the atherosclerotic plaque reduces blood flow through the afflicted artery, thereby compromising tissue or organ function distal to it.

Percutaneous transluminal coronary angioplasty is a non-surgical method for treatment of coronary atherosclerosis. In this procedure, an inflatable balloon is inserted in a coronary artery in the region of arterial narrowing. Inflation of the balloon for 15-30 seconds results in an expansion of the narrowed lumen or passageway. Because residual narrowing is usually present after the first balloon inflation, multiple or prolonged inflations are routinely performed to reduce the severity of the residual tube narrowing.

Stents are often used in combination with coronary balloon angioplasty. Typically, a stent is used to brace the blood vessel open after an initial expansion of the narrowed blood vessel by a balloon. Self expanding stents are also used to expand and hold open occluded blood vessels. Various stents and their use are disclosed in U.S. Patent Nos. 6,190,404; 6,344,055; 6,306,162; 6,293,959; 6,270,521; 6,264,671; 6,261,318; 6,241,758; 6,217,608; 6,196,230; 6,183,506; 5,989,280. The disclosure of each of these patents is incorporated in its entirety herein by reference.

One problem with angioplasty is that following the procedure restenosis, or recurrence of the obstruction, may occur. Tears in the wall expose blood to foreign material and proteins, such as collagen, which are highly thrombogenic. Resulting clots can contain growth hormones which may be released by platelets within the clot. Additionally, thrombosis may cause release of growth hormones and cytokines by cells from macrophages. Growth hormones may cause smooth muscle cells and fibroblasts to aggregate in the region and multiply. Further, following angioplasty there is often a loss of the single layer of cells that normally covers the internal surface of blood vessels which leads to thrombosis. The combination of tearing of the blood vessel wall and the loss of the endothelial layer often generates an internal blood vessel surface which is quite thrombogenic. Restenosis may result from the proliferation of smooth muscle cells, which normally reside within the arterial wall, in the area of the injury in response to the thrombosis.

Angioplasty procedures also produce injuries in the arterial wall which become associated with inflammation. Any kind of inflammatory response may cause growth of new tissue, for example, scar tissue, which may contribute to restenosis.

One of the other major causes of restenosis following angioplasty may be that the injured arterial wall may exhibit a reduced hemocompatability compared to that associated with a normal arterial wall. Adverse responses which are associated with reduced hemocompatability include platelet adhesion, aggregation, and activation; thrombosis; inflammatory cell reactions such as adhesion and activation of monocytes or macrophages; and the infiltration of leukocytes into the arterial wall.

Restenosis is a serious problem that may occur in over one third of all coronary angioplasty patients. Therefore, there exists a need for methods to reduce or eliminate the occurrence of restenosis which may follow procedures to mechanically expand an occluded blood vessel.

Botulinum toxin

The anaerobic, Gram positive bacterium Clostridium botulinum produces a potent polypeptide neurotoxin, botulinum toxin, which causes a neuroparalytic illness in humans and animals referred to as botulism. The spores of Clostridium botulinum are found in soil and can grow in improperly sterilized and sealed food containers of home based canneries, which are the cause of many of the cases of botulism. The effects of botulism typically appear 18 to 36 hours after eating the foodstuffs infected with a Clostridium botulinum culture or spores. The botulinum toxin can apparently pass unattenuated through the lining of the gut and attack peripheral motor neurons. Symptoms of botulinum toxin intoxication can progress from difficulty walking, swallowing, and speaking to paralysis of the respiratory muscles and death.